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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Wayne A Keown
500 West Cummings Park
Suite 2900
Woburn, MA 01801

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/817,374	DELORME ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6-18,23-30,32,35-39,42-44,47-49 and 57-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3,6-18,23-30,32,35-39,42-44,57-60 and 63-73* is/are allowed.

6)☒ Claim(s) *47-49, 61, 62, 74 and 75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response filed on 10/11/2006 is made of record. Claims 1, 3, 6-18, 23-30, 32, 35-39, 42-44, 47-49 and 57-75 are pending. Of which claims 1, 3, 6-18, 23-30, 32, 35-39, 42-44, 57-60 and 63-73 were allowed. In view of applicants' response, the 112 first paragraph scope of enablement rejection of claims 47-49, 61, 62, 74 and 75, made in the previous office action is maintained. In addition, new 112 first paragraph rejection is applied to these claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 47-49, 61, 62, 74 and 75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting small cell lung cancer cell histone deacetylase and treating small cell lung cancer, does not reasonably provide enablement for inhibiting any histone deacetylase and treating any or all cancer implicitly embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following apply.

The instant method of use claims 47-49, 61, 62, 74 and 75 are drawn to "inhibiting histone deacetylase" in general which implicitly as evident form page of specification includes treating various proliferative diseases.

Instant claims, as recited, are reach through claims. A reach through claim is a

claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of small cell lung cancer cell histone deacetylase by the instant compounds, instant claims reaches through inhibiting any or all histone deacetylase and treating any or all cancer in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibitor of small cell lung cancer cell histone deacetylase, based on limited assay, it is claimed that inhibiting any or all histone deacetylase and treating any or all cancers in general, which there is no enabling disclosure.

The scope of the claims as stated in page 2, includes any or all cancer due to histone deacetylase inhibition due said mode of action for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various cancers as the term cancer includes lung cancer, bone cancer, pancreatic cancer, skin cancer. cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region. stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis,

prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers, which are not adequately enabled solely based on the activity of the compounds provided in the specification. Besides the generic cancer, specification also recites a list of preferred cancers for which also there are enabling disclosure. The instant compounds are disclosed to have receptor histone deacetylase inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all cancer stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as histone deacetylase inhibitor that would be useful for all sorts of cancers and cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as psoriasis, lung cancer, brain cancer, pancreatic cancer, colon cancer etc. are very difficult to treat and despite the fact that there are many anticancer drugs.

The scope of the claims involves millions of compounds of instant claims based on the generic definition of various variable groups as well as the thousand of diseases embraced by the cancer as well as any histone deacetylase.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Rosato et al., Expert Opin. Investig. Drugs 13(1), 21-38, 2004.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors

include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating cancer that require histone deacetylase inhibitory activity.

2) The state of the prior art: Recent publications expressed that the histone deacetylase inhibition effects are unpredictable and are still exploratory. See Rosato et al., cited above especially the concluding paragraph.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating any or all cancers or proliferative diseases of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all cancers or proliferative growth and the state of the art is that the effects of histone deacetylase inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all cancers or proliferative diseases.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of proliferative diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action. Applicants' argument to overcome this rejection is not persuasive.

Thrust of applicants' argument is that down stream processing of the inhibition of histone deacetylase is not relevant to the instant method of use claims. This is not a

persuasive argument. Instant specification clearly contradicts this argument. Page 47 of specification states "

Inhibition of Histone Deacetylase

In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase represented by any one of formulae (1)-(7)."

"In some preferred embodiments, the histone deacetylase inhibitor interacts with and reduces the activity of all histone deacetylases in the cell. In some other preferred embodiments according to this aspect of the invention, the histone deacetylase inhibitor interacts with and reduces the activity of fewer than all histone

And in page 48, specification states "deacetylases in the cell. In certain preferred embodiments, the inhibitor interacts with and reduces the activity of one histone deacetylase (e.g., HDAC-1), but does not interact with or reduce the activities of other histone deacetylases (e.g., HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8). As discussed below, certain particularly preferred histone deacetylase inhibitors are those that interact with and reduce the enzymatic activity of a histone deacetylase that is involved in tumorigenesis. Certain other preferred histone deacetylase inhibitors interact with and reduce the enzymatic activity of a fungal histone deacetylase."

" Preferably, the method according to the third aspect of the invention causes an inhibition of cell proliferation of the contacted cells. The phrase "inhibiting cell

proliferation" is used to denote an ability of an inhibitor of histone deacetylase to retard the growth of cells contacted with the inhibitor as compared to cells not contacted. An assessment of cell proliferation can be made by counting contacted and non-contacted cells using a Coulter Cell Counter (Coulter, Miami, FL) or a hemacytometer. Where the cells are in a solid growth (e.g., a solid tumor or organ), such an assessment of cell proliferation can be made by measuring the growth with calipers and comparing the size of the growth of contacted cells with non-contacted cells."

Thus, it is quite clear that the intended use of the method of inhibiting histone deacetylase by the instant compounds is down stream processing, more specifically inhibition of tumorigenesis.

Hence, applicants' argument is not persuasive.

As for In re Marzocchi and other case laws cited by the applicants' they all assert an objective enablement requirement and such is not the case with instant claims. More specifically, In re Marzocchi, 439 F.2d 220,169 USPQ 367(CCPA 1971), it relates to objective enablement. Instant specification has no objective enablement treating any or all cancer mediated by histone deacetylase. Hence, In re Marzocchi, is not to the point.

Relevant passages of In re Marzocchi is presented below for applicants' careful review:

Court states: "Recitation of generic term "polyethyleneamine" must be taken as assertion by applicants that all of the "considerable number of compounds" which are included within generic term would, as a class, be operative to produce asserted enhancement of adhesion characteristics; Patent Office has no concern over breadth of

term; its only relevant concern should be over truth of such assertion; first paragraph of 35 U.S.C. 112 requires nothing more than objective enablement; how such a teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance. "

So according to court, the breadth of the term "polyethyleneamine" should not be issue. This is not the case with instant compounds. Court clearly asserts requirement for objective enablement.

Court adds further: "Turning specifically to the objections noted by the board as indicated above, it appears that these comments indicate nothing more than a concern over the breadth of the disputed term. Accepting, therefore, that the term is a generic one, its recitation must be taken as an assertion by appellants that all of the "considerable number of compounds" which are included within the generic term would, as a class, be operative to produce the asserted enhancement of adhesion characteristics.

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome

by suitable proofs indicating that the teaching contained in the specification is truly enabling.

In the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, 4 will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. Cf. In re Gazave, 54 CCPA 1524, 379 F.2d 973, 154 USPQ 92 (1967); In re Chilowsky, 43 CCPA 775, 229 F.2d 457, 108 USPQ 321 (1956)."

In the present case, specification has no objective enablement for any or all cancers mediated by histone deacetylase. Contrary to applicants urging, with the large genus of compounds and large list of cancers, one trained in the art had to extensively undue experimentation.

Hence, this rejection is proper and is maintained.

Claims 47-49, 61, 62, 74 and 75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting histone deacetylase in vitro by compounds 52i, 52k, 52l and 164 shown in Table 2, 213 & 223, does not reasonably provide enablement for inhibiting histone deacetylase in vitro by compounds of the genus of formula 1, 2 and 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Following apply.

Representative examples of structurally diverse compounds generically embraced in the invention of compound of formula 1, 2 and 3 are not shown to possess in vitro activity much less in vivo uses claimed herein. Instant compounds of formula I, 2 and 3 embrace compounds with substituents X, Y^1 , W and Z bearing plethora of structural cores and functional groups and other groups which include variously substituted monocyclic rings, bicyclic rings, tricyclic rings , spiro with variable ring sizes and variable heteroatoms variety of reactive functional groups such oxime, COOH, OH ,SH, amido, sulfoxides, sulfones, nitrile, carbamates etc. There is no reasonable basis for assuming that the myriad of compounds embraced by the claim language will all share the same bioactivity profile since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive art such as the pharmaceuticals.

Only three 4 compounds with simple substituents are shown have the said activity. And specification on page 48 states "In certain preferred embodiments, the inhibitor interacts with and reduces the activity of one histone deacetylase (e.g., HDAC-1), but does not interact with or reduce the activities of other histone deacetylases (e.g., HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8). As discussed below, certain particularly preferred histone deacetylase inhibitors are those that interact with and reduce the enzymatic activity of a histone deacetylase that is involved in tumorigenesis. Certain other preferred histone deacetylase inhibitors interact with and reduce the enzymatic activity of a fungal histone deacetylase."

Thus, there is no guarantee that instant genus of compounds, which may exceed million compounds, would interact with histone deacetylase at all and if they do so which one they would interact. Given the fact the histone deacetylases of any source (mammals , plants microorganisms) are embraced in the instant claims, one need to extensive experimentation to identify any such inhibition and the selectivity of the inhibition. In addition, the end use of such inhibition if other than treating cancer, then one need identify such an end use as specification and claims do not disclose any other use.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method of use. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds

towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Allowable Subject Matter

Claims 1, 3, 6-18, 23-30, 32, 35-39, 42-44, 57-60 and 63-73, barring finding of any prior art in a subsequent search, are allowed.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

12/26/2006